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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EDWARD D GRIEFF
HALE & DORR LLP
1455 PENNSYLVANIA AVE, NW
WASHINGTON, DC 20004

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 12/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/718,060	LETTS ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-81* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-81 are currently pending in the instant application and are subject to the following new restriction requirement. The previous restriction requirement is withdrawn in view of the following.

Response to 37 CFR 1.132 Declaration

The declaration under 37 CFR 1.132 filed 10/19/2005 by David S. Garver, Ph.D. along with applicants' arguments does not provide evidence that the compound of the formula V is within the compound of the formula (I). Specifically, the arguments provided and the opinion of David S. Garver, Ph.D., is that the proviso on page 20 of the specification does not exclude the compound of formula V because the compound of the formula V is a bis-nitrooxy, i.e. a substituted nitrooxy lower alkyl ester and that the compound of formula (V) of the present application is not encompassed by the nitrooxy lower alkyl esters. However, this is not persuasive as the proviso found in claim 1 and on page 20 of the specification states that ""X-K" in the compounds of Formula (I), does not include nitroxyl lower alkyl esters." The term "include" is considered open language and therefore, the values of "X-K" in the proviso need only "include" a nitorxyl lower alkyl ester and can therefore include other substituents. The formula's V and IX both "include" a nitroxyl lower alkyl ester in the substituents "X-K". The bis-nitrooxy of formula V includes a nitroxyl lower alkyl ester. Therefore, the application is subject to the following new restriction requirement.

Election/Restrictions

The Markush group set forth in the claims includes both independent and distinct inventions, and patentable distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentable distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentable distinct compounds, also far too numerous to list individually. **For these reasons provided below, restriction to one of the following Groups is required under 35 U.S.C. 121**, wherein a Group is a set of patentable distinct inventions of a broad statutory category (e.g. compounds, methods of use, methods of making, etc.):

I. Claims 1-2 and 53 drawn to products of the formula (I) and claims 54 and 55 drawn to the products of formula II-IV, VI-VIII and X-XVII, classified in various subclasses of classes 514, 544, 546, 548 and 549.

II. Claims 3-13 drawn to methods of use for the products of the formula (I), classified in various subclasses of class 514.

III. Claims 14 and 15 drawn to products of the formula (I) and additional therapeutic agents classified in various subclasses of 514.

IV. Claims 16-26 drawn to methods of use for the products of the formula (I) and additional therapeutic agents, classified in various subclasses of class 514.

V. Claims 27-37 and 57-66 drawn to products of the formula (I) and an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase, classified in various subclasses of classes 514.

VI. Claims 38-48 and 70-79 drawn to methods of use for the products of products of the formula (I) and an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase, classified in various subclasses of class 514.

VII. Claims 49 and 56 drawn to kits of the compound of formula (I) and formulas II-IV, VI-VIII and X-XVII, classified in class 435.

VIII. Claims 50, 51 and 52 drawn to kits of the compound of formula (I) and an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase, classified in class 435.

IX. Claim 52 drawn to kits of the compound of formula (I) and an additional therapeutic agent, classified in class 435.

X. Claims 67 and 68 drawn to products of the formula (I) along with an additional therapeutic agent and an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase, classified in various subclasses of class 514.

XI. Claims 69-79 drawn to methods of use for the products of the formula (I) along with an additional therapeutic agent and an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or

endothelium-derived relaxing factor, or is a substrate for NO synthase, classified in various subclasses of class 514.

XII. Claims 80 and 81 drawn to kits of any COX-2 inhibitor along with an additional therapeutic agent or an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase, classified in 435.

XIII. Claims 54 and 55 drawn to the products of formulas V and IX, classified in class 562.

XIV. Claim 56 drawn to kits comprising at least one compound of the formula V or IX or a pharmaceutically acceptable salt thereof classified in class 435.

In addition to an election of one of the above Groups, restriction is further required under 35 U.S.C. 121 as follows:

If Group II, IV, VI or XI is elected then election of a specific method of use is required: for example, a method of treating

A. Pain,

B. Bacterial infection,

C. Alzheimer's disease,

D. Colon Cancer, etc.

In accordance with the decisions in ***In re Harnisch***, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and ***Ex parte Hozumi***, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984), restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature

disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other member(s) obvious under 35 U.S.C. 103.

Where an election of any one of Groups I-XII is made, an election of a single compound is further required (along with a specific therapeutic agent or NO compound if part of the invention) including an exact definition of each substitution on the base molecule, wherein a single member at each substituent group or moiety is selected. For example, if a base molecule has a substituent group R1, wherein R1 is recited to be any one of H, OH , COOH, aryl, heteroaryl, alkoxy, halogen, amino, etc., then applicant must select a single substituent for R1, for example OH, phenyl, pyrazole, etc., and each subsequent variable position. In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar thereto as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim, which fall into the same class and subclass as the elected compound, but may also include additional compounds which fall in related subclasses. Examination will then proceed on the elected compound AND the entire scope of the invention encompassing the elected compound. A clear statement of the examined invention will be set forth in the first action on the merits. Note that the

restriction requirement will not be made final until such time as applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making said compound under examination. Should applicant traverse on the ground that the compound are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the compound to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other.

All compounds falling outside the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 37 C.F.R. 1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. (The provisions of 35 U.S.C. 121 apply with regard to double patenting covering divisional applications.)

Applicant is reminded that upon cancellation of claims to a nonelected invention, the inventions must be amended in compliance with 37 C.F.R. 1.48(b) if one of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(i).

If desired upon election of a single compound, applicants can review the claims and disclosure to determine the scope of the invention and can **set forth** a group of compounds which are so similar within the same inventive concept and reduction to

practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP 608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Group listed above is directed to, prepares or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over the other invention (Group), i.e. they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have bee expected to function as the structure of the claimed invention. Note that in accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product as can be seen by the instant specification, i.e. for the treatment of bacterial infection, Alzheimer's disease, colon cancer, pain, etc.

Inventions III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product as can be seen by the instant specification, i.e. for the treatment of bacterial infection, Alzheimer's disease, colon cancer, pain, etc.

Inventions V and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different

process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product as can be seen by the instant specification, i.e. for the treatment of bacterial infection, Alzheimer's disease, colon cancer, pain, etc.

Inventions X and XI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the product as claimed can be used in a materially different process of using that product as can be seen by the instant specification, i.e. for the treatment of bacterial infection, Alzheimer's disease, colon cancer, pain, etc.

Inventions I, III, V, VII, VIII, IX, X, XII, XIII and XIV are independent and distinct products which differ materially in structure and composition as the products of inventions III, IX, contain compounds of the formula (I) along with additional therapeutic agents, inventions I and VII are products of the formula (I), inventions V and VIII contain compounds of the formula (I) along with additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase, invention X contains the compound of the formula (I) along with a therapeutic agent and an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase, and

invention XII is any COX-2 inhibitor (not limited to formula (I) with a therapeutic agent or an additional compound that donated, transfers or releases nitric oxide, or induces the production of endogenous NO or endothelium-derived relaxing factor, or is a substrate for NO synthase. Furthermore, the compounds of invention XIII differ from the compounds of Invention I as the compounds of invention XIII include nitroxyl lower alkyl esters in X-K.

Inventions II, IV, VI and XI are independent and distinct methods which require independent and distinct products as described above.

In addition, because of the plethora of classes and subclasses in each of the Groups, a serious burden is imposed on the examiner to perform a complete search of the defined areas. Furthermore, a search for one group is not required for another group. Therefore, because of the reasons given above, the restriction set forth is proper and not to restrict would impose a serious burden in the examination of this application.

Advisory of Rejoinder

The following is a recitation of M.P.E.P. 821.04, Rejoinder:

> Where product and process claims drawn to independent and distinct inventions are presented in the same application, applicant may be called upon under 35 U.S.C. 121 to elect claims to either the product or process. See MPEP § 806.05(f) and § 806.05(h). The claims to the nonelected invention will be withdrawn from further consideration under 37 CFR 1.142. See MPEP § 809.02(c) and § 821 through § 821.03. However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined.
>
> Where the application as originally filed discloses the product and the process for making and/or using the product, and only claims directed to the product are presented for examination, when a product claim is found allowable, applicant may present claims directed to the process of making and/or using the patentable product by way of amendment pursuant to 37 CFR 1.121. In view of the rejoinder procedure, and in order to expedite prosecution, applicants are encouraged to present such process claims, preferably as dependent claims, in the application at an early stage of prosecution. Process claims which depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance. Amendments submitted after final rejection are governed by 37 CFR

> 1.116. Process claims which do not depend from or otherwise include the limitations of the patentable product will be withdrawn from consideration, via an election by original presentation (see MPEP § 821.03). Amendments submitted after allowance are governed by 37 CFR 1.312. Process claims which depend from or otherwise include all the limitations of an allowed product claim and which meet the requirements of 35 U.S.C. 101, 102, 103, and 112 may be entered.
>
> Where product and process claims are presented in a single application and that application qualifies under the transitional restriction practice pursuant to 37 CFR 1.129(b), applicant may either: (A) elect the invention to be searched and examined and pay the fee set forth in 37 CFR 1.17(s) and have the additional inventions searched and examined under 37 CFR 1.129(b)(2); or (B) elect the invention to be searched and examined and not pay the additional fee (37 CFR 1.129(b)(3)). Where no additional fee is paid, if the elected invention is directed to the product and the claims directed to the product are subsequently found patentable, process claims which either depend from or include all the limitations of the allowable product will be rejoined. If applicant chooses to pay the fees to have the additional inventions searched and examined pursuant to 37 CFR 1.129(b)(2) even if the product is found allowable, applicant would not be entitled to a refund of the fees paid under 37 CFR 1.129(b) by arguing that the process claims could have been rejoined. 37 CFR 1.26(a) states that "[T]he Commissioner may refund any fee paid by mistake or in excess of that required. A change of purpose after the payment of a fee...will not entitle a party to a refund of such fee..." In this case, the fees paid under 37 CFR 1.129(b) were not paid by mistake nor paid in excess, therefore, applicant would not be entitled to a refund. In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101,102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action. Form paragraphs 8.42 through 8.44 should be used to notify applicant of the rejoinder of process claims which depend from or otherwise include all the limitations of an allowable product claim.
>
> In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

The following is a recitation from paragraph five, "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. §103(b)" (1184 TMOG 86(March 26, 1996)):

> "However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim **depends from or otherwise includes all the limitations of** an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined." (emphasis added)

Therefore, in accordance with M.P.EP 821.04 and In re Ochiai, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims with process claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until, such time, a restriction between product

claims and process claims is deemed proper. Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution to maintain either dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600
12/6/05

December 6, 2005

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER